Exhibit E

UROGYNECOLOGY

Mesh contraction: myth or reality?

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OBJECTIVE: Mesh implants are widely used in surgery for female pelvic organ prolapse. Mesh shrinkage is thought to be common and caused by immunological processes. In this longitudinal study, we examined mesh dimensions at 2 time points after implantation.

STUDY DESIGN: We analyzed translabial 4-dimensional ultrasound (US) volume datasets of women seen 3-52 months after anterior compartment mesh. Datasets of first and last postoperative appointments were analyzed, with the operator blinded against all other data.

RESULTS: Forty women were assessed at least twice, comprising 59.6 woman-years. Thirty-seven of 40 (93%) were satisfied at their last appointment. Eighteen of 40 considered themselves cured, and 18 of 40 felt improved. Objective recurrence (cystocele stage 2 or greater) was seen in 16 of 40. Midsagittal mesh length increased significantly (35.8 vs 32.7; $P = .006$), and coronal mesh diameters increased nonsignificantly (37.4 vs 36.6 mm; $P = .44$).

CONCLUSION: Over an observation period of almost 60 woman-years, we found no evidence of mesh contraction.

Key words: contraction, 3-dimensional ultrasound, female pelvic organ prolapse, mesh, translabial ultrasound

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Mesh implants are widely used in surgery for female pelvic organ prolapse. Complications such as erosion and pain syndromes are not uncommon,[1] but so is recurrence of prolapse, which provided the motivation for the development of mesh kits in the first instance. Up to one third of all prolapse procedures are performed for recurrence.[2] Anterior compartment recurrence seems to be a particular problem,[3] and this seems associated with previous recurrence, prolapse severity[4] and with major trauma to the levator ani muscle (avulsion).[5]

Mesh implantation may be the only way to achieve acceptable success rates in women at high risk of recurrence,[6] although the effect of commercially available mesh kits on prolapse recurrence is unknown because of a lack of randomized controlled intervention trials.[7] Although there have been calls for such a trial in the United Kingdom,[8] such a trial is unlikely to be useful clinically unless major predictors of failure are accounted for as confounders.[6]

It has recently been claimed that mesh contraction is a common cause of mesh-related pain, erosion, and recurrence, which is held by some authors to be due to immunological processes rather than surgical methods or technique.[9] Some authors have claimed that wide-weave polypropylene mesh may contract 10% per year, reaching a 85% reduction in volume by year 8.[10] If this was true, one would have to seriously question the basis for mesh use in prolapse surgery.

It is claimed that new meshes are needed to reduce contraction and the complications supposedly associated with mesh shrinkage,[9] which would have substantial consequences regarding research and development. In this longitudinal study, we attempted to determine whether mesh contraction occurs after Perigee (American Medical Systems, Minnetonka, MN) transobturator mesh placement. This implant was the first transobturator mesh used in prolapse surgery, invented in 2004 by Ajay Rane and Malcolm Frazer, and it has become the template for all other anterior compartment meshes used since.

Materials and Methods

As part of an ongoing audit of prolapse surgery, we analyzed ultrasound volume datasets obtained from women attending follow-up appointments 3 months to 5 years after Perigee mesh placement at our hospital. Perigee mesh augmentation of anterior colporrhaphy had been performed in standardized fashion according to the manufacturer's instruction, with the difference that we remove the tail of the mesh entirely before implantation. This leaves an almost square piece of mesh between the anchoring arms, of approximately 5.0×3.7 cm^2 in area. In all cases the mesh was anchored to underlying tissues cranially and caudally, using between 1 and 3 sutures to fix the mesh margin to the bladder base.

Postoperative assessments included a local, nonvalidated questionnaire that comprised questions regarding patient

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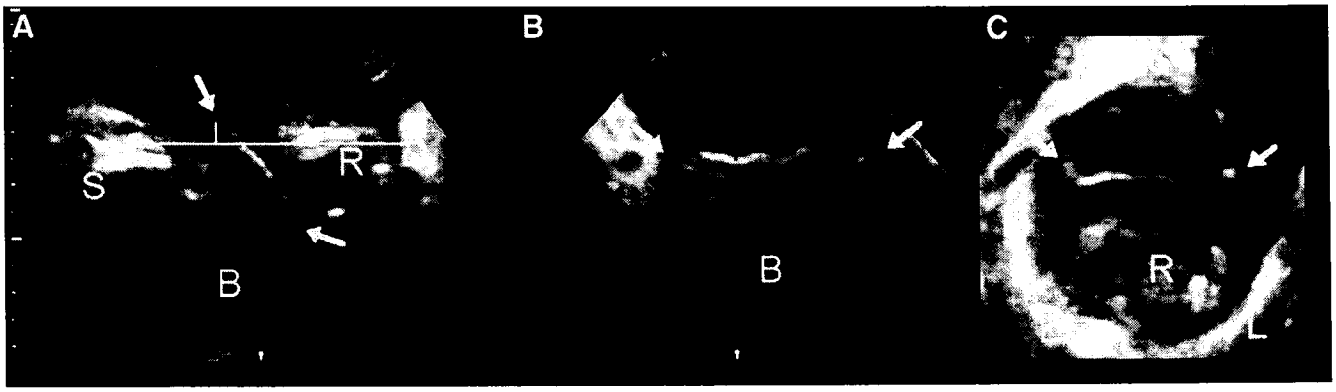
FIGURE
Identification of Perigee mesh on Valsalva



Identification of Perigee (American Medical Systems, Minnetonka, MN) mesh on Valsalva (**A**, midsagittal plane, **B**, coronal plane, and **C**, axial plane). *Arrows* show mesh length in the midsagittal (*left*) and the coronal plane (*center* and *right*). The *horizontal line in the left image* is a line of reference placed through the inferior symphyseal margin. The *vertical line* illustrates maximal descent of the caudal mesh margin on Valsalva.

S, symphysis; *B*, bladder; *R*, rectum; *L*, levator ani.

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satisfaction (yes/no/not sure) and subjective perception of cure (cured/improved/ same/worse). The clinical examination was performed in the supine position after bladder emptying, using the prolapse quantification system of the International Continence Society (ICS) Pelvic Organ Prolapse Quantification System (POP-Q), and objective recurrence was defined as a cystocele stage 2 according to this system. Patients were examined by translabial ultrasound as previously described, at rest, on maximal Valsalva and on pelvic floor muscle contraction, supine and after bladder emptying.[11] Great care was taken to avoid levator coactivation.[12]

The datasets of the first (minimum 3 months) and last postoperative appointments (maximum 4.6 years) were selected and analyzed using the postprocessing software 4D View (GE Medical; Kretz Ultrasound, Zipf, Austria), with the operator blinded against all clinical data and against the order in which the volumes had been obtained. For volumes obtained during the first and last 12 months of the observation period, the operator (M.E.) was also blinded against all calendar dates contained in the volume datasets, making it impossible to deduce the order of assessments.

Measurements of mesh location and maximum descent were taken relative to the symphysis pubis, similar to the methodology used for determining pelvic organ descent.[13] For this purpose a line is placed horizontally through the inferior margin of the symphysis pubis, and the location of the most caudal mesh margin is determined relative to this line. Mesh dimensions were determined in the midsagittal and coronal plane, as illustrated in the Figure. Occasionally in women with a large recurrent rectocele, volumes obtained on maximal Valsalva did not allow full visualisation of superior aspects of the mesh. In such cases we used volumes obtained on submaximal Valsalva.

This study was approved by the local human research ethics committee (Sydney West Area Health Service Human Research Ethics Committee reference 09-03) as a quality assurance project. Statistical analysis was undertaken using Minitab version 13 (Minitab Inc, State College, PA) and SPSS version 17 (SPSS Inc, Chicago IL). Normality testing was performed using the Kolmogorov-Smirnov method. We used intraclass correlations (single measures, absolute agreement definition) for repeatability testing and paired Student *t* tests for comparison of normally distributed continuous data obtained at different time points in the same patients.

A power calculation based on the assumption of 10% shrinkage per year demonstrated in the study published by Letouzey et al[10] suggested a sample size of 50 woman-years (ie, number of patients observed multiplied by average interval between postoperative assessments) to give 80% power to detect a 10% reduction in mesh diameters as statistically significant at the $P = .05$ level. A $P < .05$ was taken to indicate statistical significance.

RESULTS

Interobserver repeatability data (n = 20) showed moderate to excellent repeatability for the measures of mesh position and dimensions used by us (between M.E. and H.P.D., Table 1). Of a total of 63 women who were recipients of a Perigee mesh between May 2005 and March 2009, 40 women were identified whom we had assessed at least twice. In total, our data comprises 59.6 woman-years, exceeding the requirement of the power calculation by almost 20%.

Mean age at last follow-up was 63.7 (range, 34–83) years. All but 1 patient were vaginally parous. A large proportion had had concomitant procedures: 17 sacrospinous colpopexies, 14 Monarc suburethral slings, 9 posterior repairs, 7 vaginal hysterectomies, and 6 Apogee mesh repairs. Thirty-seven of 40 women (93%) were satisfied with the outcome of

TABLE 1
Repeatability of parameters of mesh location and mesh dimensions (n = 20)

Parameter, cm	Mean (operator 1)	Mean (operator 2)	ICC	95% confidence interval
Lower mesh margin at rest	1.45	1.04	0.65	0.29–0.85
Lower mesh margin on Valsalva	−0.75	−0.95	0.89	0.72–0.96
Mesh length (midsagittal) at rest	3.41	3.28	0.63	0.27–0.84
Mesh length on Valsalva	3.41	3.26	0.48	0.08–0.76
Coronal mesh diameter on Valsalva	3.71	3.77	0.49	0.07–0.76
Maximal thickness at caudal margin	0.21	0.26	0.24	0.2–0.6

ICC, intraclass correlation coefficient (absolute agreement definition, single measures).

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their procedure at their last appointment. Two were not satisfied, and 1 was not sure. Eighteen of 40 considered themselves cured, and 18 of 40 felt improved. Four felt the same or worse. Seven had required further surgery in the interim (repeat Perigee after the last follow-up included in this series [n = 2], prolapse procedure in other compartments [n = 2], excision of erosion [n = 1], and suburethral sling [n = 2]).

Objective prolapse recurrence (cystocele ICS POP-Q stage 2 or higher) was observed in 16 of 40 patients, but only 11 of 40 noticed a recurrent lump. Table 2 shows a comparison of measurements obtained at the first and last appointments. It is evident that there is no support in our data for the hypothesis that mesh retracts or shrinks over time. On the contrary, there was a significant increase in mesh length, both at rest (P = .021) and on maximal Valsalva (P = .006) at the second visit, on average 18 months after the first. On average, the mesh was slightly lower at rest (P = .005) at the second visit, and there was a weak trend in the same direction on Valsalva, suggesting that there may be slow progression toward recurrent prolapse in some women.

Comment

The increasing use of mesh in pelvic reconstructive surgery since the development of the Perigee transobturator mesh by Rane and Fraser in 2004 has caused major ongoing controversies in urogynecology. Mesh-related chronic pain and mesh erosion are significant complications that have attracted considerable attention lately.[9]

Ultrasound is the method of choice for assessing intravaginal mesh because polypropylene meshes are highly echogenic and very difficult to impossible to image with plain x-ray, computed tomography, or magnetic resonance.[14,15] This holds true for suburethral slings as well as for anterior and posterior compartment meshes.[16] Translabial, introital, and vaginal ultrasound have all been used for this purpose. In some cases mesh appears folded and/or contracted after implantation, and in general mesh surfaces seem smaller than prior to surgery.

Animal data support the contention that mesh implants shrink in vivo,[17] but to date all claims of mesh shrinkage, retraction, or contraction have been based on studies using single time points (ie, not on the longitudinal observation of individual patients).[10,14,18] One small longitudinal study suggested that most of the difference between in vitro and in vivo mesh dimensions was due to surgical technique (ie, folding and warping of the mesh during or immediately after implantation).[19]

This would also explain findings obtained a few weeks after implantation, such as reported elsewhere[14] because it is implausible that biological processes should change appearances so much within a few weeks. However, on considering the physiological processes of

TABLE 2
Comparison of mesh position and size at first and last postoperative appointment (n = 40)

Parameter, cm	First postoperative appointment	Last postoperative appointment	*P* value
Lower mesh margin at rest	+18.5 (7.4) mm	+14.6 (8.5) mm	.005
Lower mesh margin on Valsalva	−2.7 (10.9) mm	−5.1 (11.5) mm	.240
Mesh length (midsagittal) at rest	32.7 (4.9) mm	35.1 (5.7) mm	.021
Mesh length on Valsalva	32.7 (4.5) mm	35.8 (6.1) mm	.006
Coronal mesh diameter on Valsalva	36.6 (4.2) mm	37.4 (4.3) mm	.444
Maximal thickness at caudal margin	2.0 (0.6) mm	2.0 (0.6) mm	.902

Paired Student *t* test. Mean interval was 18 months.

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wound healing and observations from animal studies, it seems likely that there is some degree of wound contraction within the first few months after mesh implantation, and this is consistent with data in the imaging literature.[19]

In this longitudinal study after Perigee transobturator mesh implantation, we found no evidence of mesh shrinkage beyond 3 months after implantation. Over an observation span of almost 60 woman-years, there was no evidence of a reduction in mesh diameters. On the contrary, midsagittal mesh length at rest and on Valsalva seems to have increased by almost 10% over a period of 18 months on average. If mesh contraction exists, it is unlikely to be a progressive phenomenon and is probably limited to the period of physiological wound healing. However, to exclude mesh shrinkage/retraction or contraction as a pathophysiologically relevant process, longer observation periods in a larger number of patients will be required.

In conclusion, we have not observed any evidence of mesh shrinkage in 40 women after Perigee mesh implantation, followed up for an average of 18 months, starting 3 months after implantation. On the contrary, there may be a mild degree of downward displacement and stretching of the mesh over time. This implies that surgical technique and implant dimensions are likely to play a larger role than biological processes in explaining contracted appearances on mesh assessment postoperatively. It may be premature to enshrine the concept of mesh contraction in standardization documents dealing with mesh complications. ■

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